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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Heterocyclic bisphosphonic acid derivatives.**

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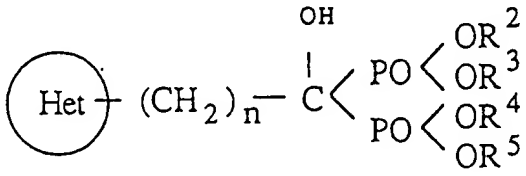
Description

The present invention relates to novel heterocyclic bisphosphonic acid derivatives and pharmaceutically acceptable salts thereof, and to bone resorption inhibitors containing them as active ingredient.

A variety of bisphosphonic acid derivatives are known, but those having a heterocyclic group as required by the present invention are novel.

We have found that the compounds of formula (I) below and pharmaceutically acceptable salts thereof are novel compounds having bone resorption-inhibitory activity as well as activity to inhibit hypercalcemia caused by bone resorption.

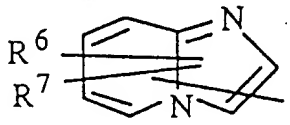
The present invention provides heterocyclic bisphosphonic acid derivatives (I) and pharmaceutically acceptable salts thereof, and pharmaceutical compositions containing them as active ingredient :



(I)

wherein

is



(B)

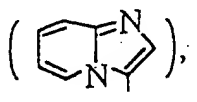
wherein R^6 and R^7 are the same or different and selected from hydroxyl and lower alkyl groups and hydrogen and halogen atoms;

R^2, R^3, R^4 and R^5 are selected from a hydrogen atom and lower alkyl groups with any two or more being the same or different; and

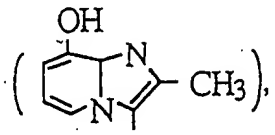
n is 0 or 1.

Herein "lower" means a linear or branched carbon chain of 1 to 5 carbon atoms if not mentioned otherwise. Thus a lower alkyl group may be a methyl, ethyl, propyl, isopropyl, butyl, isobutyl , *sec*-butyl , *tert*-butyl , pentyl(amyl), iso-pentyl or neopentyl group or the like.

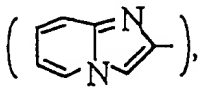
The heterocyclic group (B) may be imidazo[1, 2-a]pyridin-3-yl



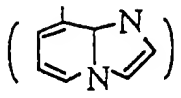
8-hydroxy-2-methylimidazo[1, 2-a]pyridin-3-yl



imidazo [1, 2-a] pyridin-2-yl



imidazo[1,2-a]pyridin-8-yl



or the like.

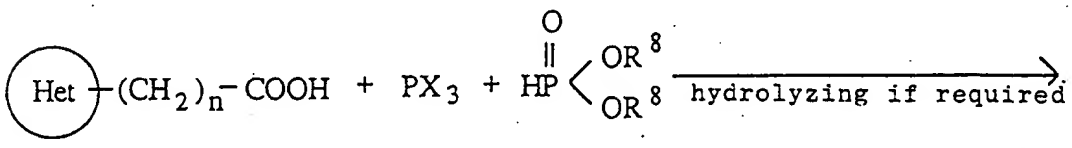
The compounds according to the present invention include tetraesters when R^2 to R^5 are lower alkyl groups, and monoesters, diesters and triesters when one to three of R^2 to R^5 is/ are lower alkyl.

The free phosphonic acids according to the present invention form salts which are included by the present invention. Preferred such salts include those with inorganic bases such as alkali metal (for example sodium, potassium)salts and alkaline earth metal (for example calcium, magnesium) salts; those with organic bases such as ammonium, methylamine, ethylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, cyclohexylamine , ethanolamine and diethanolamine salts; and those with basic amino acids such as lysine and ornithine salts and the like.

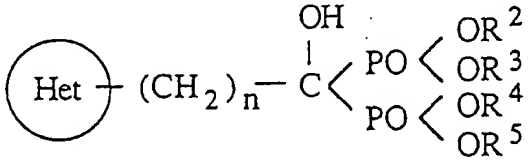
Compounds of the present invention can be prepared as follows :

Method

Compounds of the formula (I) may be made as follows:



(IV) (V) (VI)



wherein R^8 is a hydrogen atom or lower alkyl group and X is a halogen atom.

The reaction can be conducted without solvent, or in a solvent inactive to the reaction such as tetrahydrofuran, benzene, toluene, xylene or the like.

The reaction may be at or above room temperature, preferably with heating or under reflux.

The bisphosphonates obtained can be converted optionally to corresponding bisphosphonic acids by hydrolysis, generally by heating under reflux in concentrated hydrochloric acid, or by treating with strong acid or trimethylsilyl halide in a water-free solvent - e.g. in commercially available anhydrous hydrobromic acid dissolved in acetic acid or in an appropriately diluted solution thereof, or a solution of trimethylsilyl iodide in a solvent such as carbon tetrachloride, dimethylformamide, chloroform, toluene or the like. The hydrolysis can be effected under cooling or heating. For example, when the ester is hydrolyzed with trimethylsilyl halide with cooling at -10 °C or lower, a partially hydrolyzed product is obtained.

The bisphosphonic acids can be converted to their salts by treatment with a base such as sodium hydroxide, potassium hydroxide, ammonia, organic amine or the like by usual methods.

In this reaction, carboxylic acid derivative (IV) is reacted with phosphorous trihalogenide (V) and phosphorous acid (VI) or lower alkyl ester thereof. The halogen atoms may be chlorine, bromine, iodine or the like.

A mixed solution of carboxylic acid derivative (IV) and phosphorous acid or ester (VI) is heated at first at 60 to 120 °C, preferably at 80 to 110 °C,for several minutes to several hours. Then phosphorus trihalogenide (V) is added to the reacted mixed solution which is then heated at 60 to 120 °C, preferably at 80 to 110 °C,for several hours. The progress of the reaction can easily be traced by TLC (thin layer chromatography) with a developing system of chloroform-methanol.

The isolation and purification of the objective product (I) can be carried out by usual chemical treatments such as extraction, crystallization, a variety of chromatographic operations or the like.

The compounds (I) and their salts provided by the present invention have bone resorption-inhibitory activity and also activity for inhibiting hypercalcemia caused by bone resorption. In addition, they have anti-inflammatory and analgesic actions.

Experimental test methods and results below show the inhibitory effect on hypercalcemia of compound of the present invention.

Rats with hypercalcemia induced by administration of parathyroid hormone were used and the decrement of the serum calcium amount by administration of the compound was measured.

Test Method

Human 1-34 parathyroid hormone (PTH, manufactured by Peptide Laboratory) dissolved in a 0.1 % BSA (bovine serum albumin)-containing physiological saline was intravenously injected in an amount of 30 μg/kg (5 ml/kg as the solution) to 5-week-old male Wistar rats which had been fasting for 20 hours. To a normal control group, 0.1 % BSA-containing physiological saline alone was injected in the same manner. 45 minutes after the PTH injection, the rats were etherized and then subjected to celiotomy in order to collect blood from the abdominal cava with a vacuum blood-collecting tube. The blood collected was immediately centrifuged at 3000 rpm at 4 °C for 10 minutes to isolate the serum. The concentration of ionised calcium (Ca^{++}) in the serum was immediately measured in a Ca^{++} meter (Sera 250, manufactured by Horiba Manufacturing Co.).

For subcutaneous administration, compound of the present invention was dissolved in physiological saline and pH was adjusted to 7.4 with sodium hydroxide and hydrochloric acid. For oral administration, a 5 ml/kg physiological saline solution of pH 7.4 was prepared. The solutions were administered 72 hours before the PTH injection. In the same manner, physiological saline alone was administered to the normal control group and the control group.

The results for each group were expressed in terms of mean ± S. E. (standard error) and comparison was made among the groups by testing by one-way analysis of variance. The significance level was taken at 5 %.

Results

The results obtained for subcutaneous and oral administration are shown in Table 1.

Table 1

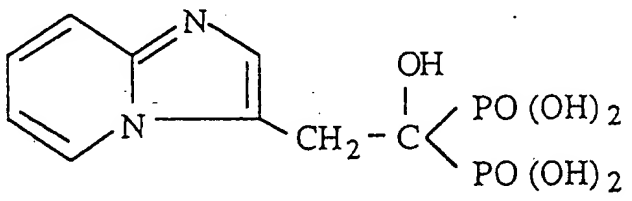
	Dose (mg/kg)	Method of Administration	N	Serum Ca^{++} (m mol/liter)
Normal Control	-	po	5	1.35±0.01
Control	-	po	5	1.43±0.01
Compound of Example 1	0.001	sc	5	1.38±0.02
	0.003	sc	5	1.26±0.02**
	0.01	sc	5	1.08±0.02**
	3	po	5	1.35±0.01
	10	po	5	1.26±0.03**
Mean value: ± S. E. *: P< 0.05 **: P< 0.01				

From the results of tests, compound according to the present invention was demonstrated to have an excellent action for reducing the amount of serum calcium. Accordingly, it is confirmed that compound of the present invention has a bone resorption inhibitory action. As diseases considered to be caused by an excessive bone-resorption, there may be mentioned Paget's disease, hypercalcemia, metastatic osteocarcinoma, and osteoporosis. Sthenic bone resorption in inflammatory arthritides such as rheumatoid arthritis is also a big problem from a clinical point of view. The compounds provided by the present invention can be used as remedial medicines for these diseases to inhibit the bone resorption and to prevent the reduction of the bone amount or to prevent or reduce the rising of the serum calcium value caused by the sthenic bone resorption.

The compounds (I) of the present invention and their salts can be used as they are or blended with any pharmaceutically acceptable carrier, vehicle, attenuant or the like to be formed into medical compositions, such as tablets, capsules, powder, granules, pills or the like for oral administration and injection solution, syrup, suppositories, ointment or the like for non-oral administration. The dosage of compounds of the present invention is, although varying with administration route, patient's symptom, etc., generally from 1 mg/day/adult to 1 g/day/adult for oral administration and from 0.1 to 10 mg/day/adult for non-oral administration.

The present invention is illustrated in more detail in the following Examples:

Example 1



2.4 g of 2-(imidazo[1,2-a]pyridin-3-yl)acetic acid•hydrochloride and 2.0 g of phosphorous acid dissolved in 25 ml of chlorobenzene were heated at 110 °C under stirring for 10 minutes. Then, 5.1 g of phosphorous trichloride was added dropwise to the mixture. The mixture was further heated under stirring for 8 hours and then chlorobenzene was decanted. 45 ml of 6N-hydrochloric acid was added to the residue and the mixture was heated under reflux for 4 hours. After cooling, the mixture was treated with activated carbon and the obtained reaction solution was concentrated under pressure. The colorless solid thus obtained was recrystallized from water-methanol to give 1.3 g of 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis-(phosphonic acid) as colorless needle-shaped crystals.

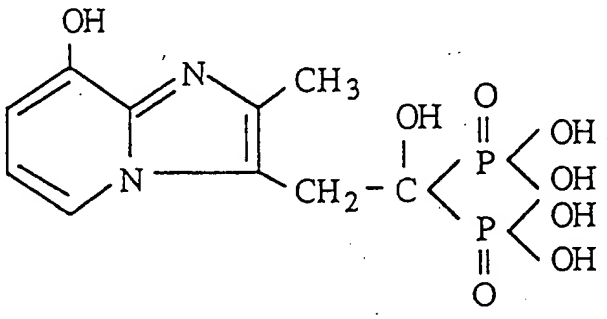
The physico-chemical characteristics of this product are as follows:

(i) m. p.: 222 to 224 °C (decomposition)
(recrystallized from MeOH-H_2O)
(ii)

Elemental Analysis (as $C_9H_{12}N_2O_7P_2 \cdot 0.5\ H_2O$) :				
	C (%)	H (%)	N(%)	P (%)
Calculated:	32.64	3.96	8.46	18.71
Found:	32.45	3.91	8.65	19.05

(iii) Mass Spectrum (m/z): FAB Mass 323 ($M^+ + 1$)
In the same manner as Example 1, the following compounds are prepared.

Example 2



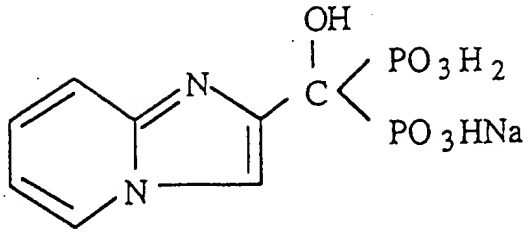
1-hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis(phosphonic acid)

Physico-chemical characteristics:
(i) m. p.: 260 to 264 °C (decomposition)
(recrystallized from MeOH-H_2O)
(ii)

Elemental Analysis (as $C_{10}H_{14}N_2O_8P_2 \cdot 1\ H_2O$) :				
	C (%)	H (%)	N(%)	P (%)
Calculated:	32.45	4.36	7.57	16.73
Found:	32.60	4.11	7.60	16.44

(iii) Mass Spectrum (m/z): FAB Mass 353 ($M^+ + 1$)

Example 3



A solution of 2.4 g of (imidazo[1,2-a]pyridin-2-yl) carbonic acid hydrochloride and 2.1 g of phosphorous acid in 25 ml of chlorobenzene was heated at 110 °C under stirring for 15 minutes and then 3.6 ml of phosphorous trichloride was added dropwise. The mixture was further heated at 110 °C under stirring for 9 hours and then chlorobenzene phase was decanted. After 30 ml of 6N-hydrochloric acid was added to the residue, the mixture was heated under reflux for 6 hours. After cooling, the resulting reaction solution was treated with activated carbon and was concentrated under reduced pressure. The residue was dissolved in 20 ml of purified water. The pH of the solution was adjusted to pH 5 with 2N solution of sodium hydroxide. Then, 30 ml of methanol was added. The mixture was left at room temperature under stirring overnight to give 0.44 g of sodium trihydrogen-1-hydroxy-1-(imidazo[1,2-a]pyridin-2-yl)methane-1,1-bis(phosphonate).

The physico-chemical characteristics of this product are as follows:

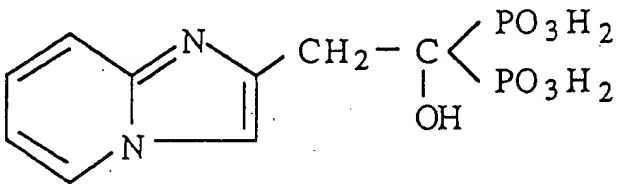
(i) m. p.: higher than 270 °C (decomposition)
(recrystallized from MeOH-H_2O)

(ii)

Elemental Analysis (as $C_8H_9N_2O_7P_2Na$):			
	C (%)	H (%)	N(%)
Calculated:	29.11	2.75	8.49
Found:	29.38	3.06	8.60

(iii) Mass Spectrum (m/z): FAB Mass 331 (M^+ + 1)

Example 4



In the same manner as Example 1, 0.2 g of 1-hydroxy-2-(imidazo[1,2-a] pyridin-2-yl)ethane-1,1-bis-(phosphonic acid) was prepared from 0.2 g of 2-(imidazo[1,2-a]pyridin-2-yl)acetic acid • hydrochloride.

Physico-chemical characteristics:

(i) Mass Spectrum (m/z) : FAB Mass 323 (M^+ + 1)

(ii) Nuclear Magnetic Resonance Spectrum (D_2O, TMS internal standard):

δ: 3.40 (2H, t, J = 12Hz),
6.94 (1H, t, J = 6Hz, pyridine ring-H),
7.20 ~ 7.60 (2H, pyridine ring-H),
7.84 (1H, s, imidazole ring-H),
8.10 ~ 8.20 (1H, pyridine ring-H)

Prescription Examples

(a) Tablet :

Compound of Example 1	5 mg
Lactose	119 mg
Corn starch	67 mg
Hydroxypropyl cellulose	4 mg
Carboxymethyl cellulose Calcium	4 mg
Magnesium stearate	1 mg
Total	200 mg

After 5 g of the compound of Example 1, 119 g of lactose and 67 g of corn starch were uniformly blended, 40 ml of 10% (w/w) aqueous solution of hydroxypropyl cellulose was added thereto and the resulting mixture was wet granulated. The granules thus obtained were blended with 4 g of carboxymethyl cellulose calcium and 1 g of magnesium stearate, and the resulting mixture shaped into tablets having a weight of 200 mg/tablet.

(b) Capsule:

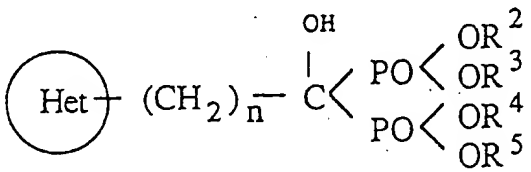
Compound of Example 1	5 mg
Crystalline Cellulose	50 mg
Crystalline lactose	144 mg
Magnesium Stearate	1 mg
Total	200 mg

The above-mentioned ingredients were blended in amounts 1,000 times those quoted and encapsulated in gelatin capsules so that one capsule contains 200 mg of the mixture.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

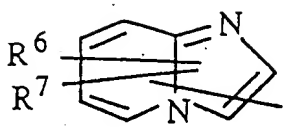
1. Heterocyclic bisphosphonic acid derivatives (I) and pharmaceutically acceptable salts-thereof



(I)

wherein

is



(B) ;

R^6 and R^7 are the same or different and selected from hydrogen and halogen atoms and hydroxy and C_1-C_5 alkyl groups;

R^2, R^3, R^4 and R^5 are selected from a hydrogen atom and C_1-C_5 alkyl groups, with any two or more being the same or different; and

n is 0 or 1.

2. A compound according to claim 1 which is 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis-(phosphonic acid), or a pharmaceutically acceptable salt thereof.

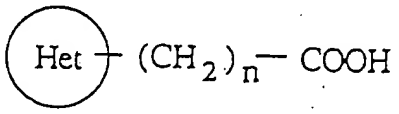
3. A compound according to claim 1 which is 1-hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)-ethane-1,1-bis(phosphonic acid) or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 which is sodium trihydrogen-1-hydroxy-1-(imidazo[1,2-a]pyridin-2-yl)-methane-1,1-bis(phosphonate).

5. A compound according to claim 1 which is 1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)ethane-1,1-bis-(phosphonic acid) or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition containing as active ingredient at least one compound according to any one of claims 1 to 5.

7. A process for preparing a compound according to claim 1 which comprises reacting carboxylic acid derivative (IV):



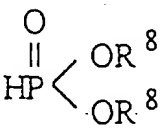
(IV) ;

phosphorus trihalogenide (V) :

PX_3 (V)

wherein X represents a halogen atom, and

phosphite or a C_1-C_5 alkyl ester (VI) :



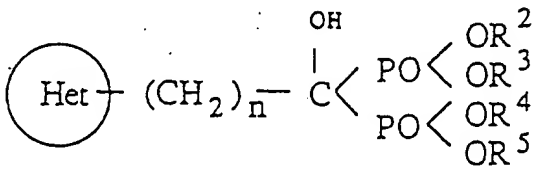
(VI)

wherein R^8 represents a hydrogen atom or C_1-C_5 alkyl group, and then optionally hydrolizing the resulting compound.

8. A process according to Claim 7 wherein R^2, R^3, R^4, R^5 , R^6 and R^7 are hydrogen atoms and n is 1.

9. A process according to claim 7 or 8 which includes converting the product to salt form.

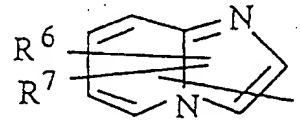
10. Use of compound selected from heterocyclic bisphosphonic acid derivatives of formula (I) and pharmaceutically acceptable salts thereof for the manufacture of a medicament having bone resorption-inhibiting activity:



(I)

wherein

is



(B) ;

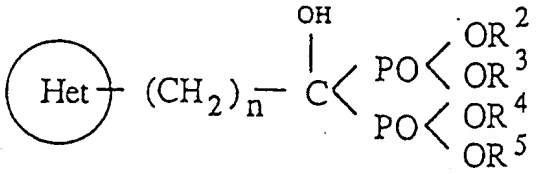
R^6 and R^7 are the same or different and selected from hydrogen and halogen atoms and hydroxy and C_1-C_5 alkyl groups;

R^2, R^3, R^4 and R^5 are selected from a hydrogen atom and C_1-C_5 alkyl groups, with any two or more being the same or different;

and n is 0 or 1; said compound including compound according to any one of claims 1 to 5.

Claims for the following Contracting States : ES, GR

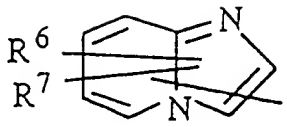
1. A method for producing heterocyclic bisphosphonic acid derivatives (I) and pharmaceutically acceptable salts thereof :



(I)

wherein

is



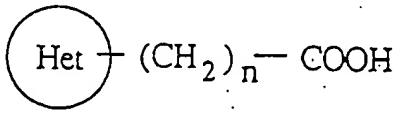
(B) ;

R^6 and R^7 are the same or different and selected from hydrogen and halogen atoms and hydroxy and C_1-C_5 alkyl groups;

R^2, R^3, R^4 and R^5 are selected from a hydrogen atom and C_1-C_5 alkyl groups, with any two or more being the same or different; and

n is 0 or 1;

which comprises reacting carboxylic acid derivative (IV) :

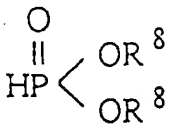


(IV) ,

phosphorus trihalogenide (V) :

PX_3 (V)

wherein X represents a halogen atom, and phosphite or a C_1-C_5 alkyl ester (VI) :



(VI)

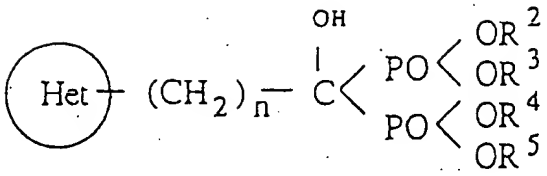
wherein R^8 represents a hydrogen atom or C_1-C_5 alkyl group, and then optionally hydrolizing the resulting compound, and optionally converting the resulting product to salt form.

2. A method according to claim 1 wherein R^2, R^3, R^4, R^5, R^6 and R^7 are hydrogen atoms and n is 1.

3. A method according to claim 1 for producing 1-hydroxy-2-imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis-(phosphonic acid), 1-hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis-(phosphonic acid), or 1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)ethane-1,1-bis(phosphonic acid) or pharmaceutically acceptable salts thereof which comprises reacting [i] phosphorous trichloride, [ii] phosphorous acid and [iii] 2-(imidazo[1,2-a]pyridin-3-yl)acetic acid hydrochloride, or2-8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)-acetic acid hydrochloride, or 2-(imidazo[1,2-a]pyridin-2-yl)acetic acid hydrochloride respectively.

4. A method according to claim 1 for producing sodium trihydrogen-1-hydroxy-1-(imidazo[1,2-a]pyridin-2-yl)methane-1,1-bis(phosphonate) which comprises reacting (imidazo[1,2-a]pyridin-2-yl)carbonic acid hydrochloride, phosphorous trichloride and phosphorous acid and reacting the resulting product with sodium hydroxide.

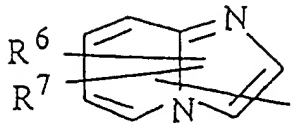
5. A method for producing a pharmaceutical composition which comprises mixing compound selected from heterocyclic bisphosphonic acid derivatives (I) and pharmaceutically acceptable salts thereof with pharmaceutical carrier:



(I)

wherein

is



(B) ;

R^6 and R^7 are the same or different and selected from hydrogen and halogen atoms and hydroxy and C_1-C_5 alkyl groups;

R^2, R^3,R^4 and R^5 are selected from a hydrogen atom and C_1-C_5 alkyl groups, with any two or more being the same or different; and

n is 0 or 1.

6. A method according to claim 5 wherein said compound is

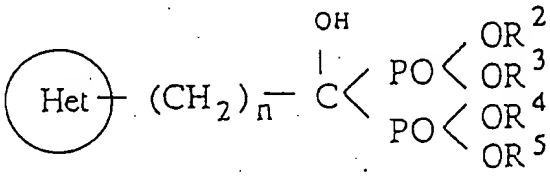
1-hydroxy-2-[imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis(phosphonic acid), or a pharmaceutically acceptable salt thereof, or

1-hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis(phosphonic acid), or a pharmaceutically acceptable salt thereof,

sodium trihydrogen-1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)methane-1,1-bis(phosphonate), or

1-hydroxy-1-(imidazo[1,2-a]pyridin-2-yl)ethane-1,1-bis(phosphonic acid) or a pharmaceutically acceptable salt thereof.

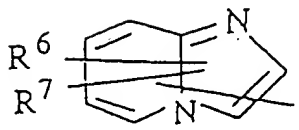
7. Use of compound selected from heterocyclic bisphosphonic acid derivatives (I) and pharmaceutically acceptable salts thereof for the manufacture of a medicament having bone resorption-inhibitory activity:



(I)

wherein

is



(B) ;

R^6 and R^7 are the same or different and selected from hydrogen and halogen atoms and hydroxy and C_1-C_5 alkyl groups;

R^2, R^3, R^4 and R^5 are selected from a hydrogen atom and C_1-C_5 alkyl groups, with any two or more being the same or different; and

n is 0 or 1.

8. Use according to claim 7 wherein said compound is

1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis(phosphonic acid), or a pharmaceutically acceptable salt thereof, or

1-hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis(phosphonic acid), or a pharmaceutically acceptable salt thereof,

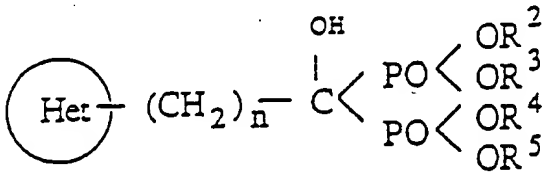
sodium trihydrogen-1-hydroxy-1-(imidazo[1,2-a]pyridin-2-yl)methane-1,1-bis(phosphonate), or

1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)ethane-1,1-bis(phosphonic acid) or a pharmaceutically acceptable salt thereof.

Patentansprüche

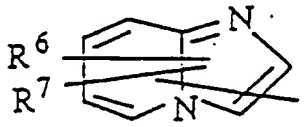
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Heterocyclische Bisphosphonsäure-Derivate (I) und pharmazeutisch annehmbare Salze davon



(I)

worin



(B) ist;

R^6 und R^7 gleich oder verschieden sind und aus Wasserstoff- und Halogenatomen und aus Hydroxy- und C_1-C_5-Alkylgruppen gewählt sind;

R^2, R^3, R^4 und R^5 aus einem Wasserstoffatom und C_1-C_5-Alkylgruppen gewählt sind, wobei zwei oder mehrere beliebige gleich oder verschieden sind; und n 0 oder 1 ist.

2. Verbindung nach Anspruch 1, welche 1-Hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)-ethan-1,1-bis-(phosphonsäure) oder ein pharmazeutisch annehmbares Salz davon ist.

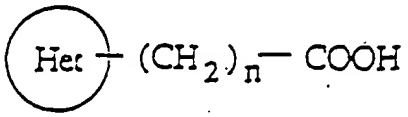
3. Verbindung nach Anspruch 1, welche 1-Hydroxy-2-(8-hydroxy-2-methylimidazo-[1,2-a]pyridin-3-yl)-ethan-1,1-bis(phosphonsäure) oder ein pharmazeutisch annehmbares Salz davon ist.

4. Verbindung nach Anspruch 1, welche Natriumtrihydrogen-1-hydroxy-1-(imidazo-[1,2-a]pyridin-2-yl)-methan-1,1-bis(phosphonat) ist.

5. Verbindung nach Anspruch 1, welche 1-Hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)-ethan-1,1-bis-(phosphonsäure) oder ein pharmazeutisch annehmbares Salz davon ist.

6. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil mindestens eine Verbindung nach einem der Ansprüche 1 bis 5 enthält.

7. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches das Umsetzen von Carbonsäure-Derivat (IV):

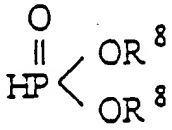


(IV)

Phosphortrihalogenid (V):

PX_3 (V)

worin X ein Halogenatom bedeutet; und
Phosphit oder einem C_1-C_5-Alkylester (VI):



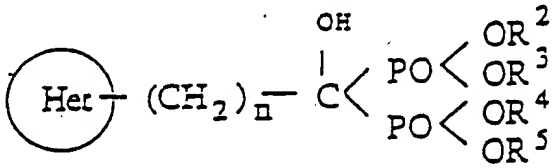
(VI)

worin R^8 ein Wasserstoffatom oder eine C_1-C_5-Alkylgruppe bedeutet und das wahlfreie Hydrolisieren der resultierenden Verbindung umfaßt.

8. Verfahren nach Anspruch 7, worin R^2, R^3, R^4, R^5, R^6 und R^7 Wasserstoffatome sind und n 1 ist.

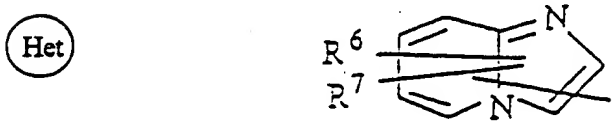
9. Verfahren nach Anspruch 7 oder 8, welches das Umwandeln des Produktes in die Salzform umfaßt.

10. Verwendung der aus heterocyclischen Bisphosphonsäure-Derivaten der Formel (I) und pharmazeutisch annehmbaren Salzen davon zur Herstellung eines Arzneistoffes mit einer die Knochenresorption inhibierenden Wirkung:



(I)

worin

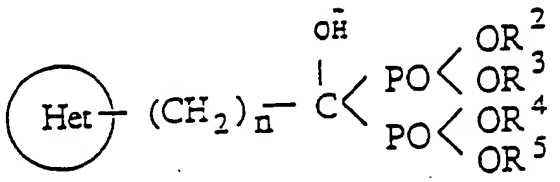


(B) ist;

R^6 und R^7 gleich oder verschieden sind und aus Wasserstoff- und Halogenatomen und aus Hydroxy- und C_1-C_5-Alkylgruppen gewählt sind;
R^2, R^3, R^4 und R^5 aus einem Wasserstoffatom und C_1-C_5-Alkylgruppen gewählt sind, wobei zwei oder mehrere beliebige gleich oder verschieden sind; und n 0 oder 1 ist; wobei die Verbindung die Verbindung gemäß einem der Ansprüche 1 bis 5 einschließt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

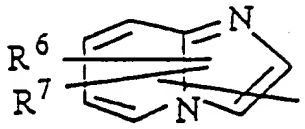
1. Verfahren zur Herstellung heterocyclischer Bisphosphonsäure-Derivate (I) und pharmazeutisch annehmbarer Salze davon:



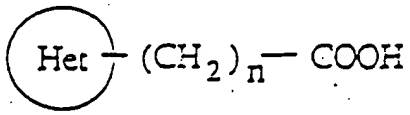
(I)

worin

(B) ist:



R^6 und R^7 gleich oder verschieden sind und aus Wasserstoff- und Halogenatomen und aus Hydroxy- und C_1-C_5-Alkylgruppen gewählt sind:
R^2, R^3, R^4 und R^5 aus einem Wasserstoffatom und C_1-C_5-Alkylgruppen gewählt sind, wobei zwei oder mehrere beliebige gleich oder verschieden sind; und n 0 oder 1 ist, welches die Umsetzung eines Carbonsäurederivats (IV):

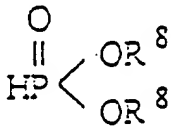


(IV) ,

eines Phosphortrihalogenids (V):

PX_3 (V)

wobei X für ein Halogenatom steht und
eines Phosphits oder eines C_1-C_5-Alkylesters (VI):



(VI)

wobei R^8 für ein Wasserstoffatom oder eine C_1-C_5-Alkylgruppe steht, und dann gegebenenfalls die Hydrolysierung der erhaltenen Verbindung und gegebenenfalls die Umwandlung des erhaltenen Produkts in die Salzform umfaßt.

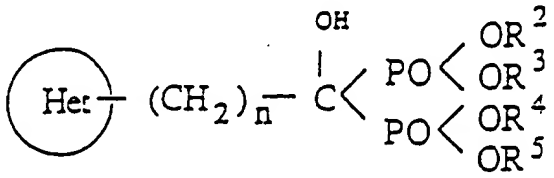
2. Verfahren nach Anspruch 1, wobei R^2, R^3, R^4, R^5, R^6 und R^7 Wasserstoffatome sind und n 1 ist.

3. Verfahren nach Anspruch 1, zur Herstellung von 1-Hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethan-1,1-bisphosphonsäure, 1-Hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)ethan-1,1-bisphosphonsäure, oder 1-Hydroxy-2-(imidazo[1;2-a]pyridin-2-yl)ethan-1,1-bisphosphonsäure oder pharmazeutisch annehmbarer Salze davon, welches die Umsetzung von [i] Phosphortrichlorid, [ii] Phosphorsäure und

[iii] 2-(Imidazo[1,2-a]pyridin-3-yl)-essigsäurehydrochlorid oder 2-(8-Hydroxy-2-methylimidazo-[1,2-a]-pyridin-3-yl)essigsäurehydrochlorid oder 2-(Imidazo-[1,2-a]pyridin-2-yl)essigsäurehydrochlorid jeweils umfaßt.

4. Verfahren nach Anspruch 1 zur Herstellung von Natriumtriwasserstoff-1-hydroxy-1-(imidazo[1,2-a]-pyridin-2-yl)methan-1,1-bis(phosphonat), welches die Umsetzung von Imidazo[1,2-a]-pyridin-2-yl)-kohlensäurehydrochlorid, Phosphortrichlorid und Phosphorsäure und die Umsetzung des erhaltenen Produktes mit Natriumhydroxid umfaßt.

5. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches die Vermischung einer Verbindung, ausgewählt aus heterocyclischen Bisphosphonsäurederivaten (I) und pharmazeutisch annehmbaren Salzen davon mit einem pharmazeutischen Trägermaterial umfaßt:



(I)

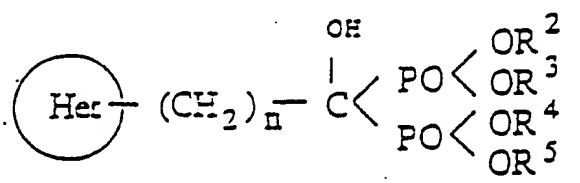
worin

(B) ist;

R^6 und R^7 gleich oder verschieden sind und aus Wasserstoff- und Halogenatomen und aus Hydroxy- und C_1-C_5-Alkylgruppen gewählt sind;
R^2, R^3, R^4 und R^5 aus einem Wasserstoffatom und C_1-C_5-Alkylgruppen gewählt sind, wobei zwei oder mehrere beliebige gleich oder verschieden sind; und n 0 oder 1 ist.

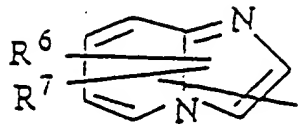
6. Verfahren nach Anspruch 5, wobei die Verbindung 1-Hydroxy-2- (imidazo [1,2-a]pyridin-3-yl)ethan-1,1-bisphosphonsäure oder ein pharmazeutisch annehmbares Salz davon oder
1-Hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyyridin-3-yl)ethan-1,1-bisphosphonsäure oder ein pharmazeutisch annehmbares Salz davon,
Natriumtriwasserstoff-1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)methan-1,1-bisphosphonat, oder
1-Hydroxy-1-imidazo[1,2-a]pyridin-2-yl)ethan-1,1-bisphosphonsäure oder ein pharmazeutisch annehmbares Salz davon ist.

7. Verwendung einer Verbindung, ausgewählt aus heterocyclischen Bisphosphonsäurederivaten (I) und pharmazeutisch annehmbaren Salzen davon zur Herstellung eines Arzneimittels mit einer die Knochenresorption inhibierenden Wirkung:



(I)

worin

Het  (B) ist:

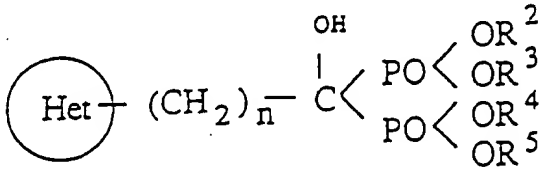
R^6 und R^7 gleich oder verschieden sind und aus Wasserstoff- und Halogenatomen und aus Hydroxy- und C_1-C_5-Alkylgruppen gewählt sind;
R^2, R^3, R^4 und R^5 aus einem Wasserstoffatom und C_1-C_5-Alkylgruppen gewählt sind, wobei zwei oder mehrere beliebige gleich oder verschieden sind; und n 0 oder 1 ist,

8. Verwendung nach Anspruch 7, wobei die Verbindung 1-Hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethan-1,1-bisphosphonsäure oder ein pharmazeutisch annehmbares Salz davon, oder
1-Hydroxy-2-(8-hydroxy-2-methylimidazo[1,2-a]pyridin-3-yl)ethan-1,1-bisphosphonsäure oder ein pharmazeutisch annehmbares Salz davon,
Natriumtriwasserstoff-1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)methan-1,1-bisphosphonat oder
1-Hydroxy-1-(imidazo[1,2-a]pyridin-2-yl)ethan-1,1-bisphosphonsäure oder ein pharmazeutisch annehmbares Salz davon ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

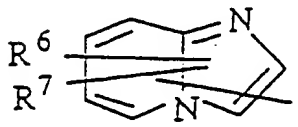
1. Dérivés hétérocycliques d'acide bis-phosphonique (I) et leurs sels pharmaceutiquement acceptables

 (I)

où

Het

est

 (B) ;

R^6 et R^7 sont identiques ou différents et choisis parmi des atomes d'hydrogène et d'halogène et des groupes hydroxy et alkyles en C_1-C_5 ;
R^2, R^3, R^4 et R^5 sont choisis parmi un atome d'hydrogène et des groupes alkyles en C_1-C_5, avec deux quelconques ou plus étant identiques ou différents ; et n est 0 ou 1.

2. Un composé selon la revendication 1 qui est l'acide 1-hydroxy-2-(imidazo[1,2-a]pyridine-3-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables.

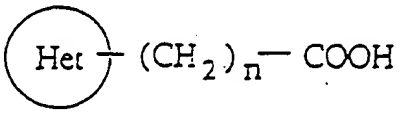
3. Un composé selon la revendication 1 qui est l'acide 1-hydroxy-2-(8-hydroxy-2-méthylimidazo[1,2-a]-pyridine-3-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables.

4. Un composé selon la revendication 1 qui est le trihydrogène-1-hydroxy-1-(imidazo[1,2-a]pyridine-2-yl)-méthane-1,1-bis phosphonate de sodium.

5. Un composé selon la revendication 1 qui est l'acide 1-hydroxy-2-(imidazo[1,2-a]pyridine-2-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables.

6. Une composition pharmaceutique contenant en tant qu'ingrédient actif au moins un composé selon l'une quelconque des revendications 1 à 5.

7. Un procédé de préparation d'un composé selon la revendication 1 qui comprend la réaction d'un dérivé d'acide carboxylique (IV)

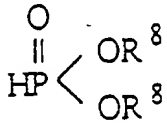


(IV)

du trihalogénure de phosphore (V)

PX_3 (V)

où X représente un atome d'halogène et
un phosphite ou un ester d'alkyle en C_1-C_5 (VI)



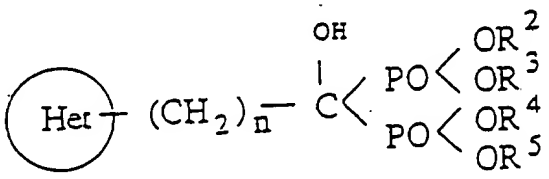
(VI)

où R^8 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_5, et ensuite l'hydrolysation optionnelle du composé résultant.

8. Un procédé selon la revendication 7 dans lequel :
R^2, R^3, R^4, R^5, R^6 et R^7 sont des atomes d'hydrogène et n est 1.

9. Un procédé selon l'une des revendications 7 ou 8 qui comprend la conversion du produit sous forme de sel.

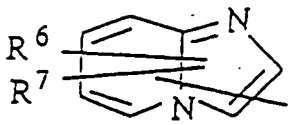
10. Utilisation d'un composé choisi parmi les dérivés hétérocycliques de l'acide bis-phosphonique de formule (I) et leurs sels pharmaceutiquement acceptables pour la fabrication d'un médicament ayant une activité d'inhibition de la résorption osseuse :



(I)

où

est

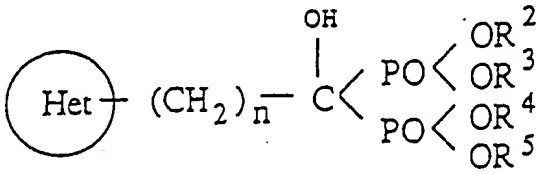


(B)

R^6 et R^7 sont identiques ou différents et choisis parmi des atomes d'hydrogène et d'halogène et des groupes hydroxy et alkyles en C_1-C_5 ;
R^2, R^3, R^4 et R^5 sont choisis parmi un atome d'hydrogène et des groupes alkyles en C_1-C_5 avec deux quelconques ou plus étant identiques ou différents ; et n est 0 ou 1 ; ledit composé incluant le composé selon l'une quelconque des revendications 1 à 5.

Revendications pour les Etats contractants suivants : ES, GR

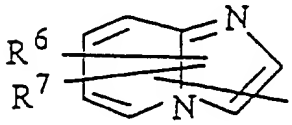
1. Un procédé pour produire des dérivés hétérocycliques d'acide bis-phosphonique (I) et leurs sels pharmaceutiquement acceptables :



(I)

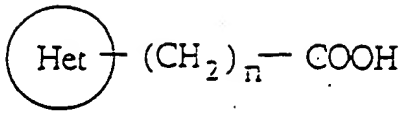
où

est



(B) ;

R^6 et R^7 sont identiques ou différents et choisis parmi des atomes d'hydrogène et d'halogène et des groupes hydroxy et alkyles en C_1-C_5 ;
R^2, R^3, R^4 et R^5 sont choisis parmi un atome d'hydrogène et des groupes alkyles en C_1-C_5 avec deux quelconques ou plus étant identiques ou différents ; et n est 0 ou 1 ;
qui comprend
la réaction d'un dérivé d'acide carboxylique (IV)

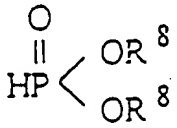


(IV) ,

du trihalogénure de phosphore (V) :

PX_3 (V)

où X représente un atome d'halogène et
un phosphite ou un ester d'alkyle en C_1-C_5 (VI)



(VI)

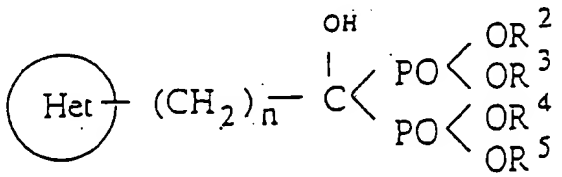
où R^8 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_5,
et ensuite l'hydrolysation optionnelle du composé résultant, et optionnellement la conversion du produit résultant sous forme de sel.

2. Un procédé selon la revendication 1 dans lequel :
R^2, R^3, R^4, R^5, R^6 et R^7 sont des atomes d'hydrogène et n est 1.

3. Un procédé selon la revendication 1 pour produire l'acide 1-hydroxy-2-(imidazo[1,2-a]pyridine-3-yl)-éthane-1,1-bis-phosphonique, l'acide 1-hydroxy-2-(8-hydroxy-2-méthylimidazo[1,2-a]pyridine-3-yl)-éthane-1,1-bis-phosphonique ou l'acide 1-hydroxy-2-(imidazo[1,2-a]pyridine-2-yl)éthane-1,1-bis-phosphonique ou leurs sels pharmaceutiquement acceptables qui comprend la réaction [i] du trichlorure phosphoreux, [ii] de l'acide phosphoreux et [iii] de l'hydrochlorure d'acide 2-(imidazo[1,2-a]pyridine-3-yl)acétique, ou de l'hydrochlorure d'acide 2-(8-hydroxy-méthylimidazo[1,2-a]pyridine-3-yl)acétique ou de l'hydrochlorure d'acide 2-(imidazo[1,2-a]pyridine-2-yl)acétique respectivement.

4. Un procédé selon la revendication 1 pour produire le trihydrogène-1-hydroxy-1-(imidazo[1,2-a]pyridine-2-yl)méthane-1,1-bis phosphonate de sodium qui comprend la réaction de l'hydrochlorure d'acide (imidazo[1,2-a]pyridine-2-yl)carbonique, du trichlorure phosphoreux et de l'acide phosphoreux et la réaction du produit résultant avec l'hydroxyde de sodium.

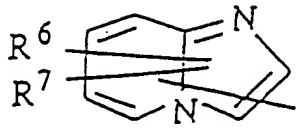
5. Un procédé pour produire une composition pharmaceutique qui comprend le mélange d'un composé choisi parmi les dérivés hétérocycliques bis-phosphoniques (I) et leurs sels pharmaceutiquement acceptables avec un support pharmaceutique



(I)

où

est

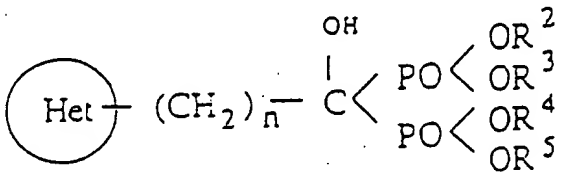


(B) ;

R^6 et R^7 sont identiques ou différents et choisis parmi des atomes d'hydrogène et d'halogène et des groupes hydroxy et alkyles en C_1-C_5 ;
R^2, R^3, R^4 et R^5 sont choisis parmi un atome d'hydrogène et des groupes alkyles en C_1-C_5 avec deux quelconques ou plus étant identiques ou différents ; et n est 0 ou 1.

6. Un procédé selon la revendication 5 dans lequel ledit composé est
l'acide 1-hydroxy-2-(imidazo[1,2-a]pyridine-3-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables ou
l'acide 1-hydroxy-2-(8-hydroxy-2-méthylimidazo[1,2-a]pyridine-3-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables ou
le trihydrogène-1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)méthane-1,1-bis phosphonate de sodium ou
l'acide 1-hydroxy-1-(imidazo[1,2-a]pyridine-2-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables.

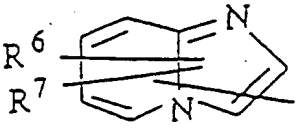
7. Utilisation d'un composé choisi parmi des dérivés hétérocycliques de l'acide bis-phosphonique de formule (I) et leurs sels pharmaceutiquement acceptables pour la fabrication d'un médicament ayant une activité d'inhibition de la résorption osseuse :



(I)

où

est



(B) ;

R^6 et R^7 sont identiques ou différents et choisis parmi des atomes d'hydrogène et d'halogène et des groupes hydroxy et alkyles en C_1-C_5 ;
R^2, R^3, R^4 et R^5 sont choisis parmi un atome d'hydrogène et des groupes alkyles en C_1-C_5 avec deux quelconques ou plus étant identiques ou différents ; et n est 0 ou 1.

8. Utilisation selon la revendication 7 dans laquelle ledit composé est
l'acide 1-hydroxy-2-(imidazo[1,2-a]pyridine-3-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables ou
l'acide 1-hydroxy-2-(8-hydroxy-2-méthylimidazo[1,2-a]pyridine-3yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables ou
le trihydrogène-1-hydroxy-2-(imidazo[1,2-a]pyridine-2-yl)méthane-1,1-bis phosphonate de sodium ou

l'acide 1-hydroxy-1-(imidazo[1,2-a]pyridine-2-yl)éthane-1,1-bis-phosphonique ou un de ses sels pharmaceutiquement acceptables.